CUTANEOUS MALIGNANCY

Duality of the Immune Response in Cancer: Lessons Learned from Skin

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The skin not only acts as a physical barrier to pathogens and toxins, but also functions as an immunological barrier constantly responding to environmental insults (e.g., UV radiation, chemical carcinogens, and oncogenic viruses). Resident and recruited immune cells respond to these types of insults by directly or indirectly inducing secretion of damage response molecules (e.g., proinflammatory cytokines, chemokines, matrix remodeling enzymes, reactive oxygen mediators, and so on) in an attempt to clear damaged cells and pathogens such that tissue homeostasis can be reinstated. Instead, when damage is chronic and/or results in somatic alterations leading to altered proliferative or apoptotic programming of epithelial cells, inflammation that was initially an acute response instead becomes chronic. In this scenario, chronic inflammation acts as a promoting force that fosters early neoplastic progression and underscores data revealing that chronic exposure to environmental toxins and pathogens is a risk factor for cancer development (Coussens and Werb, 2002).

How does activation of what should be an acute response instead foster neoplasia? The series of events discussed above is initiated by tissue-resident innate immune cells (dendritic cells, mast cells, macrophages, and γδ T cells) responding to damage response proteins, including damage-associated molecular patterns, pathogen-associated molecular patterns, Toll-like receptor ligands, colony stimulating factors, cytokines (tumor necrosis factor-α), and chemokines released from ''damaged'' epithelial cells (Balkwill *et al.*, 2005; Balkwill, 2009). Upon engagement of these damage signals, resident immune cells are activated, and they respond by degranulation or secretion of a diversity of mediators that in turn results in activation of resident mesenchymal support cells (fibroblasts, adipocytes, mural, and endothelial cells), recruitment of peripheral blood leukocytes into ''damaged'' tissue, as well as engagement of cells of the adaptive immune system, both locally and peripherally (Balkwill *et al.*, 2005). Dendritic cells, and to a lesser extent macrophages, are antigen-presenting cells that activate B and T cells to mount an adaptive immune response. Upon antigen recognition, B cells, as well as $CD4^+$ and $CD8^+$ T cells, undergo clonal expansion and mount responses specific to presented antigens. Although all of these tissue responses are otherwise entirely ''normal,'' during early neoplasia, they fail to resolve (Dvorak, 1986). Thus, chronic inflammation underlies the earliest stages of cancer development (Balkwill and Mantovani, 2001; Coussens and Werb, 2001, 2002). As such, chronic inflammation is now accepted as a hallmark of cancer development (Hanahan and Weinberg, 2011), where both innate and adaptive immune cells exert either pro- or anti-tumor activities dependent on their activation state and the microenvironment in which they reside (Balkwill *et al.*, 2005; de Visser *et al.*, 2006; Hanahan and Coussens, 2012). Although early studies of skin focused on the suppressive effects of leukocytes on carcinogenesis, we now recognize that proliferation and survival of epithelial cells harboring genomic alterations are sustained by chronic inflammatory pathways; understanding the nuances of these support mechanisms has yielded a diversity of new anticancer targets currently being utilized in the clinic.

ANTITUMOR PROPERTIES OF IMMUNE CELLS

The antitumor activities of immune cells were first harnessed in the late nineteenth century when Coley injected bacterial mixtures as therapy for sarcomas after noting that cancer patients who had subsequently acquired acute infections developed spontaneous tumor regression (Coley, 1891). Although the basis for tumor regression was not understood at the time, it was the first evidence that the immune system could be harnessed for cancer therapy; we now know that cytotoxic T cells were responsible for Coley's observed tumor regressions (Bickels *et al.*, 2002). More recent studies reporting antitumor roles for the immune system are clinical studies reporting that organ transplant recipients receiving long-term immunosuppressants exhibit increased relative risk for squamous cell carcinomas (Hardie *et al.*, 1980; Hartevelt *et al.*, 1990). It has subsequently been revealed that increased relative risk is in part because of major histocompatibility complex class I and II genes responsible for antigen presentation to cytotoxic T cells (Bouwes Bavinck *et al.*,

1991a, b), as well as infections by human papilloma viruses and UV exposure in a setting where T cells are incapable of responding (de Visser *et al.*, 2006).

Studies led by Schreiber and colleagues were among the first to characterize tumor-specific antigens. These studies revealed that $CD8^+$ T cells become licensed by specific tumor antigens, thus representing structures against which antitumor immune responses are elicited (Schreiber *et al.*, 1988; Ward *et al.*, 1989). Antigens in this form represent protein products of mutant genes, overexpressed genes, or viral genes (Cheever *et al.*, 2009). However, the immune system is also continually sculpting tumors (i.e., immunoediting), as was evidenced by work from Schreiber *et al.* (2011). Immunoediting occurs in three stages: elimination, equilibrium, and escape. The elimination phase consists of the innate and adaptive arms of the immune system working in concert to destroy cancer cells. In the event that mutated cells are not eliminated, the equilibrium phase ensues wherein leukocytes interact with neoplastic cells and maintain a state of dormancy. The escape phase is entered once neoplastic cells become less immunogenic, evade host immune responses, or actively immunosuppress the host, resulting in tumor outgrowth and progression (Schreiber *et al.*, 2011).

The functional significance of cytotoxic T lymphocytes in skin carcinogenesis was first revealed in a UV-induced experimental tumor model in which depletion of $CD8^+$ T cells correlated with enhanced tumor growth in immunocompetent mice (Fortner and Kripke, 1977). Cytotoxic $CD8^+$ T cells respond to tumor-specific antigens and mediate antitumor responses via expression of IFN-γ and granzymes. Progressing tumors (escape phase) often overcome cytotoxic T-cell specificity by reducing expression of IFN-γ receptors, loss of antigen expression, and reduced major histocompatibility complex expression. Although IL-10 has historically been thought to contribute to immunosuppressive environments and reduced antitumor activity, it was recently reported that IL-10 in skin induces $CD8^+$ T-cell tumor infiltration, directly leading to increased expression of IFN-γ, granzymes, and intratumoral major histocompatibility complex molecules, thereby restoring tumor immunosurveillance in late-stage tumors (Mumm *et al.*, 2011; Emmerich *et al.*, 2012). Another mechanism by which $CD8^+$ T cells and natural killer T cells can escape immunosurveillance was revealed using mice overexpressing the stress antigen major histocompatibility complex class Ib molecule Rae-1. $CD8^+$ T cells and natural killer T cells express the Rae-1 receptor NKG2D, and thus recognize and lyse damaged cells expressing Rae-1 (Oppenheim *et al.*, 2005). Overexpression of Rae-1, representing chronically stressed cells, results in downregulation of NKG2D on $CD8^+$ T cells and natural killer T cells, thus rendering them anergic and enabling immune evasion, thereby increasing cancer incidence and progression (Girardi *et al.*, 2004; Oppenheim *et al.*, 2005). Together, these studies indicate that immunosurveillance and response to tumor antigens is a critical aspect of cancer suppression/regression.

Langerhans cells (LCs) residing in epidermal layers of squamous epithelium are thought to represent initial antigen-presenting cells encountering tumor antigens (Lewis *et al.*, 2010). LCs sample their surrounding microenvironment for antigens, and upon encountering such, traffic via dermal lymphatic vessels to skin-draining lymph nodes where they present antigen to T cells (Lewis *et al.*, 2010). Their protective role against carcinogenesis was initially demonstrated by Grabbe *et al.* (1991) using *in vivo* models. Epidermal cells from control mice and Thy-1-depleted epidermal cells were preincubated with tumor fragments. Cell suspensions were then injected into syngeneic mice and when challenged with tumor cells, neither the untreated epidermal cells nor the Thy-1-depleted epidermal cells were protected against tumor challenge, indicating that LCs participated in antitumor immunity (Grabbe *et al.*, 1991). However, it should be noted that this role may be dependent on the tumor context, as it has recently been reported that LCs are also responsible for metabolism of 7,12-dimethylbenz [α]anthracene (DMBA) into its mutagenic metabolite DMBA-trans-3,4-diol; mice lacking LCs are resistant to DMBA-induced carcinogenesis and exhibit reduced DNA damage, including fewer *HRas* mutations (Strid *et al.*, 2008; Modi *et al.*, 2012).

The γδ T cells (dendritic epidermal T cells) are resident epithelial T cells expressing restricted or invariant TCR-γ and -δ genes. In murine epidermis, dendritic epidermal T cells function in immunosurveillance; they respond to stress and other self-antigens expressed by damaged or diseased keratinocytes, and they directly lyse damaged cells (Kaminski *et al.*, 1993; Girardi, 2006). The role of dendritic epidermal T cells in tumor immunosurveillance was highlighted by Girardi *et al.* (2001), where they revealed increased susceptibility to cutaneous malignancies induced by DMBA/12-*O*-tetradecanoylphorbol-13-acetate (TPA) in γδ T cell–deficient mice. One mechanism by which dendritic epidermal T cells may regulate tumor development in this context is via NKG2D recognition of the stress ligand Rae1 that is induced upon DMBA/TPA treatment (Girardi *et al.*, 2001). As is the case with the $CD8^+$ T cells described above, γδ T cells expressing NKG2D can kill Rae-1-expressing cells *in vitro*, thus demonstrating their cytolytic activity toward damaged and stressed cells (Girardi *et al.*, 2001; Oppenheim *et al.*, 2005).

PROTUMOR PROPERTIES OF IMMUNE CELLS

Although the antitumor properties of the immune system are well appreciated, there is now also ample evidence that select subtypes of leukocytes also promote tumorigenesis. Virchow first reported the presence of leukocytes in tumors in the nineteenth century and hypothesized that tumors arise at sites of chronic inflammation (Balkwill and Mantovani, 2001). Although later studies have confirmed the link between chronic inflammation and increased

incidence of tumor development (Balkwill and Mantovani, 2001), the functional role of immune cells in tumorigenesis has only recently begun to be elucidated.

Among the first immune cells recognized as having a protumoral role in neoplastic progression were mast cells, based on *in vivo* studies in the K14-HPV16 mouse model of squamous carcinogenesis (Coussens *et al.*, 1999). Mast cells were found to release matrix remodeling proteolytic enzymes, including mast cell protease-4 and -6 and matrix metalloprotease-9, that in turn activate fibroblasts and initiate angiogenesis (Coussens *et al.*, 1999, 2000). Subsequent studies elucidated mechanisms by which myeloid cells, including mast cells and macrophages, are recruited to premalignant tissue and foster ongoing tumor development. B cells, which are activated in the periphery by antigen-presenting cells, secrete autoantibodies that form circulating immune complexes that accumulate in neoplastic stroma as the vasculature becomes leaky and angiogenic (de Visser *et al.*, 2005). The circulating immune complexes interact with activating Fcγ receptors (FcγRI and III), leading to activation of FcγR-dependent signaling cascades in myeloid cells that in turn foster protumoral programs critical for cancer development (Andreu *et al.*, 2010). The significance of this process is illustrated by studies where absence of B cells in premalignant tissue or in squamous cell carcinomas of tumor-prone mice, by either genetic ablation or B-cell depletion via administration of B cell–depleting αCD20 antibody, prevents or limits circulating immune complex deposition, impedes recruitment and activation of protumoral-type leukocytes, and thereby limits neoplastic progression (Andreu *et al.*, 2010; Affara *et al.*, 2014).

Tumor necrosis factor-α is an important proinflammatory cytokine secreted by epithelial cells, mast cells, macrophages, and T cells involved in neoplastic progression of several cancer

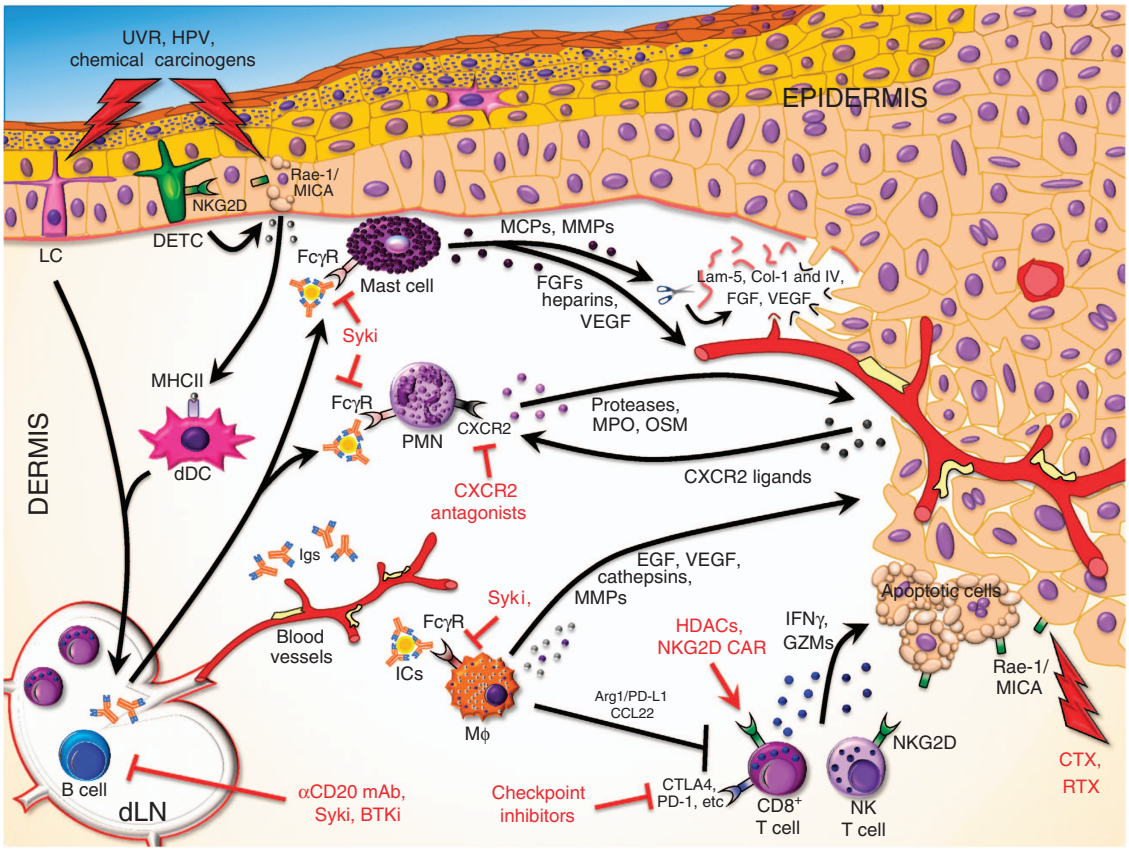

Figure 1. Putative targets for combinational immunotherapy in squamous carcinogenesis. Pro- and antitumor activities of resident and recruited immune cells during squamous carcinogenesis are depicted. Neoplastic epidermis is shown progressively acquiring invasive/malignant properties (left to right) and invading into ectopic dermis. Resident and recruited immune cells, and their effector molecules, are depicted in black, with targets for therapeutic intervention shown in red. By combining immunological targets with chemotherapy and/or radiotherapy in patients harboring favorable immunoscores, durable antitumor responses are likely to be achieved as compared with conventional cytotoxic monotherapy. Arg1, arginase-1; BTKi Bruton's tyrosine kinase inhibitor; CAR, chimeric antigen receptor T cells; Col, collagen; CTLA-4, cytotoxic T-lymphocyte antigen-4; CTX, chemotherapy; dDC, dermal dendritic cell; DETC, dendritic epidermal T cell; dLN, draining lymph node; EGF, epidermal growth factor; FcγR, immunoglobulin Fc γ receptor; FGF, fibroblast growth factors; GZM, granzyme; HDAC, histone deacetylase; HPV, human papilloma virus; IC, immune complex; Lam, laminin; LC, Langerhans cell; MΦ, macrophage; MCP, mast cell protease; MHCII, major histocompatibility class II; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NKT cell, natural killer T cell; OSM, oncostatin M; PD-L1, programmed death ligand-1; PMN, polymorphonuclear leukocyte; RTX, radiotherapy; Syki, Syk kinase inhibitor; VEGF, vascular endothelial growth factor.

types, including chemically induced squamous cancers. Mice lacking tumor necrosis factor-α are largely resistant to tumor formation following administration of DMBA/TPA (Moore *et al.*, 1999), where IL-10-secreting B regulatory cells and $CD4^+$ T cells play important roles in regulating terminal phenotypes (Schioppa *et al.*, 2011).

Other mechanisms by which immune cells can be recruited to sites of chronic inflammation are by expression of CXC chemokine receptors (CXCRs). CXCR2 is primarily expressed on neutrophils and is a key regulator of their recruitment and effector responses (Cacalano *et al.*, 1994). Cutaneous activation of protein kinase C, either by TPA or in oncogene-expressing transgenic mice, results in secretion of cytokine-induced neutrophil chemoattractant and macrophage inflammatory protein 2, leading to recruitment of $CXCR2^+$ neutrophils (Cataisson *et al.*, 2006). It has been reported that CXCR2-deficient mice exhibit reduced chemotaxis of neutrophils and a corresponding reduction in tumorigenesis in DMBA/TPA-treated mice, indicating that targeting protumorigenic neutrophils may be therapeutically efficacious (Jamieson *et al.*, 2012).

CONCLUDING REMARKS

Malignant tumors generally evolve by developing mechanisms to evade antitumor immune-based programs embedded in the tissues in which they reside, or by instead conscripting them to promote various hallmarks of carcinogenesis (Hanahan and Coussens, 2012). Based on these observations, targeted immunotherapies should strive to either enhance the antitumor properties of immune cells, mitigate the protumor properties of immune cells, or a combination of the two. Perhaps one of the most significant immunomodulating therapies recently developed with demonstrated efficacy in melanoma is an antibody to cytotoxic T lymphocyte antigen 4 (CTLA4, ipilimumab) that inhibits the negative regulatory activity of CTLA4 on cytotoxic T cells and T regulatory cells (Chambers *et al.*, 2001; Wing *et al.*, 2008). Clinical results from a randomized phase III trial for relapsed-refractory metastatic melanoma with ipilimumab indicated a 2-fold survival benefit at 12–15 months, thus leading to its recent Food and Drug Administration (FDA) approval (Hodi *et al.*, 2010). Although successes such as those observed with ipilimumab embolden immunotherapy approaches, the fact that the majority of patients receiving the drug failed to respond indicates that other protumoral mechanisms will also require targeting in order to achieve durable remissions for all patients. Combining

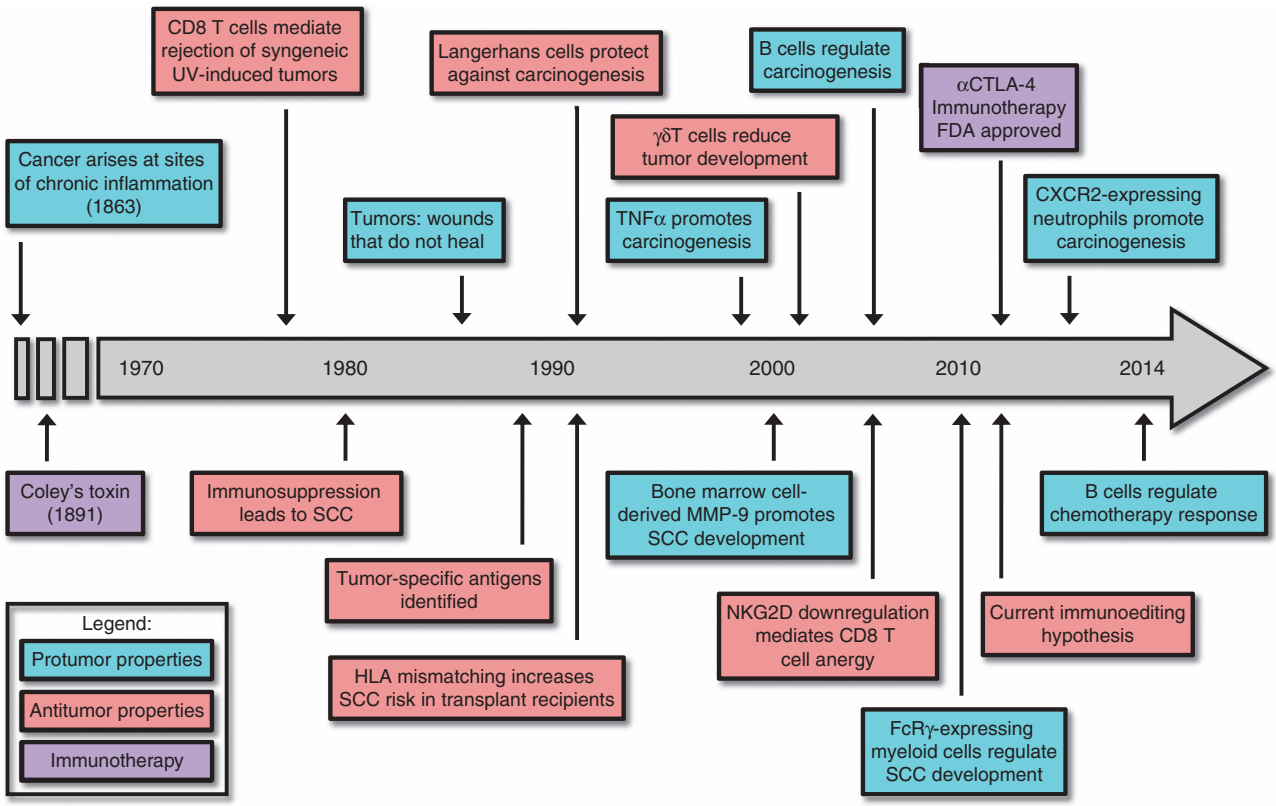

Figure 2. Timeline of milestones in skin tumor immunology that have demonstrated the pro- and antitumor properties of immune cells and their mediators. Also depicted are immunomodulating therapies that have been used in the past or have current Food and Drug Administration (FDA) approval. CTLA-4, cytotoxic T-lymphocyte antigen-4; CXCR2, CXC chemokine receptor-2; FcγR, immunoglobulin Fc γ receptor; HLA, human leukocyte antigen; MMP-9, matrix metalloproteinase-9; SCC, squamous cell carcinoma; TNF-α, tumor necrosis factor-α.

immune-based therapies with conventional chemotherapy, radiotherapy, or targeted therapy based on tumor immunometrics, e.g., immunoscore (Galon *et al.*, 2013), are likely to be the next generation of personalized cancer therapies (Coussens *et al.*, 2013), and aid in new approaches going forward (Figure 1).

The skin serves as a vital barrier between the host and a harsh environment. Resident and recruited leukocytes are constantly serving critical roles in maintaining tissue homeostasis, but in instances of chronic inflammation, they paradoxically contribute to every stage of cancer progression. The models outlined above, including UV-induced tumorigenesis, chemical carcinogenesis, and the K14-HPV16 mouse model of squamous carcinogenesis, have been indispensable for understanding the role of the immune system in cancer initiation and progression (Figure 2), and we expect many additional milestones in tumor immunology to be revealed using the skin as a model system.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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